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Examinations of social and non-social factors in the neurodevelopment of autism

A Dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Psychology by Joseph Paul McCleery

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2006
The Dissertation of Joseph Paul McCleery is approved, and it is acceptable in quality and form for publication on microfilm:

                                                               Chair

University of California, San Diego

2006
DEDICATION

This dissertation is dedicated to individuals with autism and their families. In particular, it is dedicated to the numerous children with autism who have inspired me through their uniqueness as well as their struggles; and to their parents whose hard work and dedication to their children has played a major role in my dedication to furthering our understanding of autism and related developmental disorders.
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ABSTRACT OF THE DISSERTATION

Examinations of social and non-social factors in the neurodevelopment of autism

by

Joseph Paul McCleery

Doctor of Philosophy in Psychology

University of California, San Diego, 2006

Professor Karen Dobkins, Chair

Autism is a pervasive developmental disorder characterized by deficits in social and communication skills, as well as restricted interests and repetitive behaviors, with symptom onset by 3 years of age. Recent studies have documented structural and functional abnormalities in a variety of brain regions associated with social processing and perception in this population. As a result, there is a growing belief that autism can be explained by impairment in social brain systems, and several neurodevelopmental models have been proposed to explain the social and communicative impairments of individuals with autism. The current research explores the role social and non-social factors play in the neurodevelopmental basis of autism in three studies of functional brain development. Study 1 examines social and non-social semantic integration in young children with autism by analyzing event-related potentials recorded during the processing of word and environmental sound meaning within a picture context.
Results suggest that the neural integration of word, but not environmental sound, meaning is impaired in these children, providing support for a social/non-social distinction in this area of functioning. Experiments 2 and 3 explore the early functional development of brain systems involved in face and object processing in the first year of life in autism by studying neurodevelopmental risk in infant siblings of children diagnosed with autism. Specifically, experiment 2 employs event-related potentials to examine the neural correlates of early stages of face and object processing in 10-month old infants, and experiment 3 employs visual psychophysical measures to assess the integrity of the magnocellular and parvocellular visual pathways in 6-month old infants. The results of experiment 2 suggest that familial risk for autism is associated with abnormalities in face and object processing in the first year of life. The results of experiment 3 suggest that familial risk for autism is also associated with abnormalities in the subcortical magnocellular visual pathway, which is believed to provide critical input for face processing in the first several months of life. Together, these results provide new insight into the roles social and non-social factors may play in the neurodevelopment bases of autism.
Chapter 1

Abstract

Autism is a pervasive developmental disorder characterized by deficits in social and communicative skills. Behavioral and neuroimaging studies have found that children with autism evidence semantic deficits, with particular difficulties in verbal comprehension. However, it is not currently known whether these semantic deficits are confined to the verbal domain or represent a more general problem with the processing of semantic information. Therefore, the focus of the present study was to investigate verbal and non-verbal semantic integration in young high functioning children with autism and typically developing children using event-related potentials (ERPs) to examine the N400 component. The two groups were matched on chronological age, nonverbal IQ, language age, and gender. The stimuli were matching and mismatching picture-word and picture-sound pairs. For example, a picture of a car was presented with (i) the word "car" (word match), (ii) the word "ball" (word mismatch), (iii) the sound of a car engine (sound match), or (iv) the sound of a bouncing ball (sound mismatch). The N400 was measured by subtracting matching word and sound ERPs from mismatching word and sound ERPs, and t-tests were performed to determine whether the N400 responses were different from zero. Children in both groups showed semantic integration in the environmental sound condition. However, only controls showed differentiation of matching versus mismatching words. These results demonstrate that there is a semantic integration deficit in children with autism, and that it is more severe in the verbal domain.
1.1 Introduction

Deficits and delays in language and communication abilities are a core component of autism (American Psychiatric Association, 2000), and a great deal of research has focused on the examination of language behaviors in this population (see Tager-Flusberg, Paul, & Lord, 2005 for review). Furthermore, behavioral studies that have employed multiple measures during the early school years have found language abilities to be one of the strongest predictors of both response to treatment and cognitive outcomes in individuals with autism (Sallows & Graupner, 2005; Venter, Lord, & Schopler, 1992), underscoring the importance of early language development for this population. Impairments in pragmatic aspects of language, abnormal prosody, and pronominal reversal are considered diagnostic indicators for autism spectrum disorders (ASD) (American Psychiatric Association, 2000). However, deficits and abnormalities in grammatical, syntactical, and semantic aspects of language have also been documented and are all generally believed to be affected in at least some individuals with ASD (Tager-Flusberg, Paul, & Lord, 2005).

In the realm of semantic processing, experimental examinations of school-aged children with autism have uncovered deficits in idiom comprehension (e.g., Kerbel & Grunwell, 1998), deficits in the use of word meaning for the interpretation of complex language (e.g., Tager-Flusberg, 1985), a decreased reliance on semantic versus syntactic information in sentence comprehension (Paul, Fisher, & Cohen, 1988; Tager-Flusberg, 1981), and impaired memory for semantic information (Tager-Flusberg,
1985). Data collected from adolescents and adults with autism indicate that at least some of these deficits persist with age (e.g., Paul & Cohen, 1986; Toichi & Kamio, 1998), and that subtle abnormalities in patterns of semantic abilities within and across individuals at these ages are suggestive of possible alternative strategies for semantic processing in those individuals in whom behavioral performance deficits do ultimately resolve (e.g., Kamio & Toichi, 2000; Toichi & Kamio, 2001).

Although early experimental studies did not find evidence for deficient processing of single word meaning in individuals with autism (Eskes, Bryson, & McCormick, 1990; Frith & Snowling, 1983), the results of several more recent behavioral and parent report studies indicate that word and phrase comprehension may be impaired in this population, at least during the preschool years. In 2003, Charman and colleagues used a standardized parent report measure, the MacArthur Communicative Development Inventory (CDI – Infant Form), to examine language development in preschool children with autism (Charman, Drew, Baird, & Baird, 2003). They found that these children exhibited significant delays in language abilities overall, but that they were more severely impaired in language comprehension skills relative to language production skills. Furthermore, several studies have found that impairments in receptive language in the first two years of life are among the best markers for a later diagnosis of autism (Dahlgreen & Gillberg, 1989; Landa & Garret-Mayer, 2006; Mitchell, Brian, Zwaigenbaum, Roberts, Szatmari, et al., 2006; Landa & Garrett, 2006; Zwaigenbaum, Bryson, Rogers, Roberts, Brian, et al., 2005). These data suggest the possibility that semantic
processing deficits in autism may, in fact, have roots in deficient processing of very basic semantic information early in life.

Several recent neuroimaging studies have uncovered abnormalities in the neural processing of semantic information in individuals with autism. In both 1999 and 2005, Dunn and colleagues used event-related potentials (ERPs) to examine the processing of semantic categories in auditory words in 8-year-old through 12-year-old, high-functioning children with autism and typically developing controls (Dunn & Bates, 2005; Dunn, Vaughn, Kreuzer, & Kurtzberg, 1999). Specifically, they recorded brain activity while children listened to words that were in a given category or outside of that category (e.g., animals versus non-animals). In both studies, the control children showed differential brainwave responses to words that were within the category versus those that were not, but the children with autism did not. More recently, Harris and colleagues (Harris, Chabris, & Clark,, 2006) used Functional Magnetic Resonance Imaging (fMRI) to examine brain activations during the processing of concrete and abstract auditory words in high-functioning adults with autism and typically developing controls. The individuals with autism showed abnormal activation patterns, with diminished activation in a region of frontal cortex (Broca’s area) but increased activation in a region of left temporal cortex (Wernicke’s area), relative to controls. The brain activity of the individuals with autism also showed reduced differentiation of concrete and abstract words relative to control participants. The results of these studies indicate that the neural processing of semantic information is abnormal in both children and adults with autism. However,
to date, no studies have examined the neural processing of single word meaning in children with ASD.

1.1.1 Neural Correlates of Word Meaning in Typical Children

Several electrophysiological studies have been conducted to examine the processing of single word meaning in children. Most relevant to the current study, Byrne and colleagues have used event-related potentials to examine brainwave responses to matching and mismatching picture-word pairs in children between 4 and 12 years of age (Byrne, Connolly, MacLean, Dooley, Connolly, MacLean, Dooley, Gordon, & Beattie, 1999). They presented subjects with a picture of an object followed by an auditory word that either matched the object in the picture or did not, and examined a negative brainwave component recorded from electrodes over the frontal and parietal cortices approximately 400 milliseconds following the auditory stimulus. This component, the N400, has been examined extensively in studies of semantic processing, and has proven to be a solid index of the semantic integration of an incoming word with the fore-going context (e.g., Kutas & Hillyard, 1980). Byrne and colleagues found that the N400 responses of the children in their study were larger in amplitude in response to words that did not match the picture than to those that did at all ages studied (Byrne et al., 1999). In a more recent study, Friedrich and Friederici (2004) used a similar technique to show that an N400-like component differentiates matching and mismatching words as young as 19-months of age. These
data suggest that the N400 brainwave component can be used as an index of the processing of single word meaning in very young typically developing children.

To examine the neural correlates of linguistic and non-linguistic semantic integration in young children with autism, we collected event-related potentials (ERP) data from 4- to 7-year-old, high-functioning children with autism spectrum disorders (ASD) and typically developing control children. Still images of objects (e.g., a ball) were presented on a computer monitor. A word or environmental sound that either matched or did not match the object in the picture began after a 600 ms delay. The picture and word then ended simultaneously. For example, a picture of a ball was presented with the word “ball” (word match) or the word “car” (word mismatch). Similarly, in a separate block of trials, a picture of a ball, for example, was presented with the sound of a ball bouncing (sound match) or the sound of a car engine starting (sound mismatch). The N400 component was then examined. Results indicate that semantic integration of word meaning, but not environmental sound meaning, is impaired in the children with autism. These results provide the first evidence that the semantic integration of single word meaning within a picture context is impaired early in life in children with autism, and further suggest that this semantic processing impairment may be specific to social stimuli.

1.2 Methods

1.2.1 Participants
Ten children with autism spectrum disorders and ten typically developing children participated in the study. No child had a history of seizures or other medical or neurologic disorder. All children had normal hearing and normal, or corrected to normal, vision. Children with autism were diagnosed with an autism spectrum disorder by a licensed clinical psychologist or medical doctor not associated with this research. This diagnosis was verified through administration of the Autism Diagnostic Interview – Revised (ADI-R, Lord, Rutter, & LeCouteur, 1994) and the Autism Diagnostic Observation Schedule – Generic (ADOS-G, Lord, Risi, Lambrecht, Cook, Leventhal, et al., 2000) in the laboratory by a licensed clinical psychologist. Based on the results of these assessments and clinical judgment, seven of the ten children met DSM-IV criteria for Autistic Disorder, and the remaining three met criteria for Pervasive Developmental Disorder – Not Otherwise Specified (American Psychiatric Association, 2000).

Control participants were recruited from the San Diego area. All participants scored within the normal range on a standardized test of intelligence (see Procedure below), and the ASD and control groups were matched on chronological age and gender. Handedness was assessed using parent report of child laterality preferences on the tasks utilized in the Hand Preference Demonstration Task (Soper, Satz, Orsini, Henry, Zvi, et al., 1986), which was supplemented by observation of child behavior on these tasks when parents were unsure. Using this method, five children with autism were determined to be right-handed, 3 left-handed, and 2 showed evidence of either mixed handedness or having not yet established a reliable handedness preference. In
the control group, 9 children were determined to be right-handed, none left-handed, and 1 showed evidence of either mixed handedness or having not yet established a reliable handedness preference.

1.2.2 Cognitive and Language Testing

Standardized assessments of cognitive and language skills were administered to all children. The Differential Ability Scales (Elliott, 1990) was used to assess intellectual functioning, and the Expressive One Word (EOW, Gardner, 1990a) and Receptive One Word (ROW, Gardner, 1990b) assessments were administered to provide measures of expressive and receptive language abilities, respectively. The mean standardized scores and standard errors for each group are presented in Table 1.1. One-tailed t-tests conducted on each of these measures revealed that the children with ASD scored lower on the measure of global intelligence, the Differential Abilities Scales. However, there were no significant group differences on any of the other measures (including nonverbal IQ or verbal IQ alone), and the children with autism had normal intelligence, as evidenced by a mean Intelligence Quotient above 100 (see Table 1.1).

1.2.3 Stimuli

All auditory stimuli used in this study were derived from norming studies conducted by Saygin, Dick, and Bates (2005) and Cummings and colleagues (Cummings, Ceponiene, Koyama, Saygin, Townsend, et al., in press). Briefly, 31
adult subjects listened to environmental sound stimuli presented via computer, pressed a button as soon as they recognized the environmental sound, and produced both a noun label (e.g., “ball”) and a verb label (e.g., “ball bouncing”) for that sound. Verbal responses were recorded and coded off-line by two independent coders for accuracy (0=inaccurate response, 1=related to accurate response, 2=accurate response). Only environmental sounds that were characterized by both moderate to high identifiability and short reaction times in this study were used. Word stimuli were developed based on the noun label responses of the participants in the norming study. Words produced by three North American speakers (1 female, 2 male) were digitally recorded in a sound isolated room (Industrial Acoustics Company, Inc, Winchester, UK) using a Beyer Dynamic (Heilbronn, Germany) Soundstar Mk II Unidirectional Dynamic microphone. All auditory stimuli were digitized at 44.1 kHz with a 16-bit sampling rate. All auditory stimuli were set to a mean average intensity of 65 dB. The environmental sounds used in this study varied in duration from 470-870 ms (mean = 574 ms, SD = 104 ms). Word stimuli varied in duration from 262-940 ms (mean = 466 ms, SD = 136 ms). Fifty-four pictures with 54 words and 54 environmental sounds were used in the current study (see Appendix A for lists of Word and Environmental Sound stimuli).

Visual stimuli were full-color digitized photos (480 x 480 pixels) of common action-related objects that could produce an environmental sound, and be described by a noun. All pictures were presented in the middle of the computer monitor on a gray background. The same set of pictures was used for both the matching and
mismatching picture contexts. The only constraint on the semantic mismatching trials was that the mismatch had to be unambiguous (e.g., the picture of a basketball was not presented with the sound of hitting a golf ball).

1.2.4 Behavioral Assessment

A computer-based behavioral assessment of word and environmental sound knowledge was conducted in the laboratory. In this assessment, the child sat in a comfortable chair facing two 17-inch computer monitors, which were angled slightly inward toward the child. On each trial two different pictures were simultaneously presented, one on the left monitor and one on the right monitor. Two seconds after the pictures were presented, a word or environmental sound matching one of the two pictures was played via speakers located beside both computer monitors. Following two additional seconds, the word or environmental sound was played again. The child was instructed to touch the picture that matched the word or environmental sound at any point following the presentation of the first auditory stimulus. The experimental trials were preceded by several practice trials. The stimuli presented during these practice trials were not used during the actual experiment. An experimenter sat behind the child and out of his or her view, initiated each trial by pressing the space bar, and entered the child’s left and right picture/monitor responses using a computer keyboard. Each child participated in a separate block of trials for both word stimuli (54 trials) and environmental sound stimuli (54 trials), with block order counterbalanced across subjects.
1.2.5 Electrophysiological Assessment

Matching and mismatching picture-sound pairs were presented such that the sound began 600 ms after the onset of the picture, and both stimuli ended together. The duration of the stimulus presentation varied slightly from trial to trial, due to variations in sound stimulus length (see Stimuli, above). Average trial duration was 1066 ms for the word condition (range: 862-1540), and 1174 ms for the environmental sound condition (range 1070-1470). The intertrial interval varied randomly between 1900 and 2100 ms. In separate blocks of trials, color pictures of objects were followed by either a word (i.e., a noun) or an environmental sound. All children in both experimental groups participated in both the word and environmental sounds conditions. Each child viewed two blocks of 108 trials (54 matching, 54 mismatching) of each condition (words, environmental sounds), with block order counterbalanced across subjects (i.e., words, sounds, words, sounds OR sounds, words, sounds, words). Therefore, the total number of trials presented to each child was 216 word (108 matching, 108 mismatching) and 216 environmental sound (108 matching, 108 mismatching) trials. Data were collected in an electromagnetically and acoustically shielded chamber, with the child sitting in a comfortable chair approximately 75 cm from the stimulus presentation monitor in an electromagnetically and acoustically shielded chamber. Brief breaks were taken both within and between testing blocks, and an experimenter sat next to the child and facilitated attention to the monitor whenever the child became temporarily distracted. A miniature digital video camera
located below the stimulus presentation monitor and aimed at the child’s face was used to record digital video that was then used to identify and eliminate trials during which the child was not attending to the visual stimulus off-line.

1.2.6 EEG Recording and Analysis

Continuous EEG was recorded for each subject using a stretchy knit cap with 62 electrode locations sewn into it (Biosemi, Inc, Amsterdam, Netherlands). The following electrodes were then connected to the scalp according to the International 10-10 system: AF3, AF4, AF7, AF8, AFz, C1, C2, C3, C4, C5, C6, Cz, CP1, CP2, CP3, CP4, CP5, CP6, CPz, F1, F2, F3, F4, F5, F6, F7, F8, Fz, FC1, FC2, FC3, FC4, FC5, FC6, FCz, Fp1, FT7, FT8, Iz, O1, O2, Oz, P1, P2, P3, P4, P5, P6, P7, P8, P9, P10, PO3, PO4, PO7, PO8, POz, T7, T8, TP7, TP8, and right and left mastoids. During data acquisition, all channels were referenced to the right mastoid; off-line, data were re-referenced to the average of the left- and right-mastoids.

The EEG (0.01-100Hz) data was amplified 20,000x and digitized to 256 Hz for the off-line analyses. Prior to averaging, independent component analysis (Jung, Makeig, Humphries, Lee, McKeown, et al., 2000; Jung, Makeig, Westerfield, Townsend, Courchesne, et al., 2000) was used to correct for eyeblinks and lateral movements. Sporadic artifacts (e.g., random, infrequent head or facial movements, but not consistent artifacts such as eyeblinks) were manually rejected from the data prior to ICA training in order to obtain clean components. Eyeblink and lateral eye movement artifact components were then removed from the data. Trials with
remaining sporadic artifacts were rejected using voltage thresholds (Picton, Bentin, Berg, Donchin, Hillyard, et al., 2000). EEG was low-pass filtered at 50 Hz, and high-pass filtered at 0.05 Hz, using a 2-way least squares FIR filter. Epochs time-locked to the auditory stimulus containing 87 ms pre-stimulus and 1100 ms post-stimulus time were baseline-corrected with respect to the pre-stimulus interval and averaged by stimulus type.

Trials during which the child was not attending to the visual stimuli for any portion of the trial were removed through trial-by-trial examination of the video recording. ERPs were then calculated by averaging the segments within each condition. Children with autism produced an average of 64 artifact-free trials per condition and control children produced an average of 73 artifact-free trials per condition (i.e., word match, word mismatch, environmental sound match, environmental sound mismatch). One-tailed t-tests confirmed that there were no group differences between the number of trials produced for any condition, or overall.

1.2.7 ERP Waveform Analysis

A prominent N400 component with waveform topography and scalp distribution consistent with previous studies was identified in the grand average waveforms of both matching and mismatching stimuli in both groups in both conditions. The N400 was maximal over parietal, central-parietal, central, and frontal-central electrodes. In order to examine brainwave activity associated with the differentiation of matching and mismatching picture-word and picture-sound stimuli,
N400 difference waves were generated by subtracting ERPs to matching pairs from the ERPs to mismatching pairs. Electrode groups for the word and environmental sounds conditions were chosen based on examination of both individual subject and grand average N400 difference waves. For the words condition, the following 14 central and central-parietal electrodes were selected: C1, C2, C3, C4, C5, C6, Cz, CP1, CP2, CP3, CP4, CP5, CP6, CPz. For the environmental sounds condition, the following 14 central-parietal and parietal electrodes were selected: CP1, CP2, CP3, CP4, CP5, CP6, CPz, P1, P2, P3, P4, P5, P6, Pz. Mean amplitudes during the time window of maximal differentiation, 350-500 ms, were generated for each condition for both the ASD and control groups. Finally, t-tests were conducted in order to determine whether N400 difference waves were different from zero for each group in each condition.

1.3 Results

1.3.1 Behavioral Results

There were no statistical differences in the mean percent correct between the two groups in the environmental sound (ASD mean = 99.4, s.e. = 0.003; CON mean = 100, s.e. = 0) or word (ASD mean = 99.6, s.e. = 0.002; CON mean = 98.1, s.e. = 0.001) conditions, and no child made more than 2 errors out of the 54 trials in each condition. Therefore, we surmise that all children had knowledge of the relationships between the pictures and the sounds, as well as the pictures and the words.
1.3.2 ERP Results

As presented in Figure 1.1a, both high-functioning children with ASD and typically developing control children showed evidence of semantic integration in the environmental sound condition (CON Diff = 2.36 mV, s.e. = 0.65, p < 0.05; AUT Diff = 2.28 mV, s.e. = 1.03, P < 0.05). However, as presented in Figure 1.1b, only the control children showed differentiation of matching versus mismatching words (CON Diff = 1.89 mV, s.e. = 1.03, p < 0.05; ASD Diff = 0.29 mV, s.e. = 1.03, p = 0.39).

1.4 Discussion

The present study was designed to determine whether children with autism are impaired in the ability to integrate semantic information of an incoming word within a picture context and, if so, whether this impairment is specific to linguistic stimuli or is the result of a more general impairment in semantic integration. In contrast to matched controls, high-functioning children with autism showed no difference between their responses to auditory words that matched the picture context versus those that did not. In contrast, the same subjects did exhibit a significant difference between N400 responses to environmental sounds that matched the picture context versus those that did not. These results support the hypothesis that semantic integration of single word meaning is impaired in young high-functioning children with autism. These results are particularly compelling, considering that that the ASD children were high-functioning, verbally competent, and demonstrated knowledge of the semantic relationships between the word and picture stimuli in a behavioral
assessment. Furthermore, data from a recent study suggest that N400-like responses during semantic integration of single word meaning with a picture context develop by 19 months of age in typically developing children (Friedrich & Friederici, 2004).

The finding that semantic integration of environmental sound meaning, examined using the same paradigm, was intact in this population suggests that this semantic integration deficit may be limited to, or more severe in, the linguistic and/or social domains. One possible explanation for impaired semantic integration during word, but not environmental sound, processing in the current study relates to distinctions between word and environmental sound learning.

In a recent study, Cummings and colleagues assessed word and environmental sound knowledge in 15, 20, and 25 month olds by examining visual preference for pictures of objects that matched versus mismatched and auditory word (Cummings, Saygin, Bates, & Dick, in press). Results indicated that word and environmental sound knowledge was highly similar at all ages tested, indicating that the development of word and environmentally meaningful sound knowledge have similar trajectories. However, Cummings and colleagues did find some dissociations. Specifically, environmental sound knowledge in individual children was strongly correlated with chronological age, whereas word knowledge was found to be most strongly associated with vocabulary size. These data imply that environmental sound knowledge is primarily the result of straightforward experience with object-sound relations, which increases with age. Alternatively, the development of word comprehension skills is
likely dependent upon a complexity of factors known to be associated with language learning.

A wealth of research on language learning in typically developing children has uncovered strong links between both early attention to speech (e.g., Jusczyk, 1997) and joint attention behaviors (e.g., Bates & Goodman, 1997; Carpenter, Nagell, & Tomasello, 1998; Tomasello, 1998) and language learning. In terms of word learning, shared attention with adults and attention to speech leads to repeated pairings of auditory labels (e.g., “look at the ball”) with visual objects (e.g., infant orients attention to the ball) that are believed to be critical for normal word learning (Bates & Goodman, 1997; Bates, Thal, Finlay, & Clancy, 2003; Tomasello & Farrar, 1986). Simultaneously, numerous studies have shown that children with autism exhibit reduced attention to face and voices in the natural environment relative to controls (Baranek, 1999; Dawson, Toth, Abbott, Osterling, Munson, et al., 2004; Maestro, Muratori, Cavallaro, Pei, Stern, et al., 2002; Osterling & Dawson, 1994; Osterling, Dawson, & Munson, 2002; Werner, Dawson, Osterling, & Dinno, 2000), and do not show typical patterns of preference for speech over non-speech stimuli in experimental contexts (Klin, 1999; Kuhl, Coffey-Corina, Padden, & Dawson, 2005). Young children with autism also exhibit profound deficits in responding to and initiating a class of social-communicative gestures (e.g., pointing, eye gaze) know collectively as protodeclarative joint attention (e.g., Dawson et al., 2004; Mundy, 1995). These deficits may contribute to word comprehension deficits early in life in this population,
and may ultimately result in the development of alternative strategies for the processing of word learning at the neural level in ASD.

There is also reason to believe that children with ASD find objects that provide cause-effect auditory and/or visual sensory feedback particularly reinforcing (Ingersoll, Schreibman, & Tran, 2003), which may result in enhanced experience with object-sound meanings. Therefore, this altered experience base in ASD may simultaneously decrease competence in word comprehension and increase comprehension of environmental sound meaning, resulting in impaired semantic integration of word meaning but intact semantic integration of environmental sound meaning, such as that observed in the current study.

A more direct explanation for the observed word-specific impairment in semantic integration in ASD observed in the current study is related to social attention. Specifically, the children with autism may have failed to automatically attend to the word stimuli, resulting in deficient processing at the level necessary for semantic integration of word meaning. Consistent with this possibility, two recent studies by Ceponiene and colleagues found that ERP responses associated with automatic attention were absent in response to speech stimuli but not in response to closely matched non-speech sound stimuli in ASD (Ceponiene, Lepisto, Shestakova, Vanhala, Alku, et al., 2003; Lepisto, Kujala, Vanhala, Alku, Huotilainen, et al., 2005). Experimental studies have also shown that children with autism prefer non-speech auditory stimuli to speech, whereas typically developing and developmentally delayed control children consistently preferred speech stimuli (Klin, 1999; Kuhl, Coffey-
Corina, Padden, & Dawson, 2005). Therefore, it is possible that the ASD children in the current study may have automatically attended to the non-social, non-linguistic environmental sound stimuli during the environmental sounds blocks, but not automatically attended to the word stimuli in the word blocks. Conversely, control children must have attended to the auditory stimuli in both conditions.

The data from the current study also provide insight into the neural basis of semantic processing impairments in autism. In an effort to explain failure of the N400 to distinguish within and out-of category words in children with ASD, Dunn and Bates (2005) proposed that brain overgrowth (or under-pruning) during late childhood in ASD may affect organization of the lexicon and impair automatic selection of the most compatible response. In this model, N400 responses were absent in children with ASD because the automatic selection of the most-likely candidate(s) did not occur and, therefore, there was no lexical (e.g., animal) item to be compared with other items (e.g., non-animal) at the time of the N400.

In the paradigm used in the current study of single-word processing, Dunn and Bates’ model would translate into a failure to automatically select the word “car” from other activated items (e.g., “Ford,” “police”) when presented with a picture of a car and, therefore, to fail to automatically detect the mismatch between this “car” and the word “ball” that is played during a mismatch trial. We feel this explanation is unlikely to account for the results observed in the current study. Specifically, given that behavioral data suggest that the comprehension of words and environmental sounds develop in step with one another between 15 and 25 months of age (Cummings et al.,
in press), and that N400-like responses to known words that match versus mismatch a picture context are present by 19 months of age, it seems unlikely that macrocephaly during late childhood could account for word-specific N400 semantic integration deficits in ASD like those observed in the current study.

In 2006, Harris and colleagues used fMRI to examine the neural correlates of concrete and abstract auditory word processing in adults with autism (Harris et al., 2006). The major finding of this study was that brain activations in autism were reduced in an area of frontal cortex associated with semantic processing (Broca’s area) and increased in areas of the temporal cortex associated with language and auditory processing (Wernicke’s area). These results are similar to those of a previous study on sentence comprehension in ASD (Just, Cherkassky, Keller, & Minshew, 2004), suggesting the possibility that these findings may reflect an alternative network for language processing in autism that relies less on traditional language regions in the frontal cortex and more on posterior regions. Harris and colleagues, therefore, suggested that semantic processing impairment in ASD may be associated with impaired development of frontal language areas, perhaps due to genetic or behavioral-environmental factors.

A neurodevelopmental model of impaired development of frontal language areas is potentially consistent with the results of the current study. The results of neuropsychological research on words and environmental sounds suggests there are significantly overlapping neural substrates for semantic processing of these two types of stimuli in temporal cortex (e.g., Saygin, Dick, Wilson, Dronkers, & Bates, 2003).
In terms of the N400, studies have found that environmental sound/word pairs exhibit semantic integration effects that are highly similar to those of word/word pairs (Van Petten & Rheinfelder, 1994; but see also Friedman, Cycowicz, & Dziobek, 2003). However, to date, no studies have examined contributions of frontal language regions to semantic processing of words versus environmental sounds. Therefore, if future research finds that early semantic processing of words and environmental sounds are dissociated in frontal language regions, such as Broca’s area, then abnormal development of this system in ASD may explain the current findings.

In summary, children with autism show impairments in the semantic integration of single word meaning at the neural level. Specifically, unlike typically developing control children, they failed to show a differential ERP response to words that matched a picture context versus those that did not. Alternatively, both ASD and typically developing children showed differentiation of environmental sounds that matched a picture context versus those that did not. These electrophysiological data support a growing body of behavioral evidence that suggests that impairments in word comprehension early in life are pervasive in autism, and further suggest that these impairments may be related to deficits in social and/or linguistic functioning characteristic of this population.

**Acknowledgements**

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Burner, Marisa Evans, and Jeanne Townsend. I would also like to thank Natacha Akshoomoff for administering the clinical-diagnostic assessments. Finally, I would like to thank all of the families who participated in the study.

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functioning autism: Evidence of underconnectivity. *Brain, 127*(Pt. 8), 1811-1821.


Table 1.1 Child characteristics for linguistic versus non-linguistic semantic integration experiment. Means and standard errors (in parentheses) for each of the experimental groups, and the results of statistical comparisons between groups, are presented. Statistical results are based on one-tailed t-tests.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Autism</th>
<th>Control</th>
<th>Significance Level</th>
</tr>
</thead>
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<tr>
<td>Chronological Age (Years)</td>
<td>5.9 (0.3)</td>
<td>5.9 (0.3)</td>
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</tr>
<tr>
<td>Total IQ (DAS)</td>
<td>101.4 (5.45)</td>
<td>118.6 (3.39)</td>
<td>$p &lt; 0.01$</td>
</tr>
<tr>
<td>Verbal IQ (DAS)</td>
<td>104.5 (7.99)</td>
<td>118.8 (3.85)</td>
<td>NS</td>
</tr>
<tr>
<td>Nonverbal IQ (DAS)</td>
<td>111.5 (5.33)</td>
<td>113 (4.46)</td>
<td>NS</td>
</tr>
<tr>
<td>Receptive Lang. (ROW)</td>
<td>100.5 (5.21)</td>
<td>108.1 (3.46)</td>
<td>NS</td>
</tr>
<tr>
<td>Expressive Lang. (EOW)</td>
<td>113.5 (5.91)</td>
<td>118.1 (3.15)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Figure 1.1 N400 difference scores for matching versus mismatching a) environmental sound-picture and b) word-picture pairs in children with autism (black bars) and controls (grey bars). Both children with autism and controls showed robust differences for environmental sound-picture pairs, whereas only control children differentiated matching and mismatching word-picture pairs. Error bars represent standard errors of the means, and statistical information is based on one-tailed t-tests comparing N400 difference scores to zero.
## Appendix A

<table>
<thead>
<tr>
<th>Word</th>
<th>Environmental Sound</th>
<th>Word</th>
<th>Environmental Sound</th>
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<td>Croaking</td>
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<td>hitting</td>
<td>horse</td>
<td>Galloping</td>
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<td>quacking</td>
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</tr>
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Chapter 2

Abstract

Research using event-related potentials (ERPs) has shown that individuals with autism and their family members exhibit atypicalities in early stage cortical responses during face processing. These atypicalities in face processing may be a marker for genetic susceptibility to autism, perhaps resulting from abnormalities in social or perceptual systems in the first year of life. This study investigated early stage face processing in 10-month old infants who have an older sibling diagnosed with autism and control infants with no family history of autism by examining two early stage face-sensitive brainwave components recorded over occipito-temporal cortex, the N290 and the P400. Examination of the N290 component indicated that infant siblings of children with autism showed a faster brain electrical response to objects and a larger amplitude response to objects compared to control infants. Examination of the P400 component indicated that control infants processed faces faster than objects but at-risk infants processed objects faster than faces. These findings indicate that familial risk for autism is associated with abnormalities in brain activation patterns during early stages of both face and object processing early in life.

2.1 Introduction

Autism spectrum disorders (ASD) are pervasive developmental disorders characterized by deficits in social and communication skills, which can currently be
diagnosed between 24 and 36 months of age (Filipek, Accardo, Baranek, Cook, Dawson, Gordon, et al., 1999). Decades of research on individuals diagnosed with autism have revealed abnormalities in a variety of social, communicative, and emotional behaviors (see Carter, Davis, Klin, & Volkmar, 2005; Tager-Flusberg, Paul, & Lord, 2005; and Hobson, 2005 for reviews). Concomitant with this behavioral data, significant evidence has accumulated documenting neural abnormalities in ASD, both at the structural and functional levels (see Minshew, Sweeney, & Bauman, 2005 and Schultz & Robbins, 2005 for reviews). Despite the wealth of data collected to date, very little is known about the earliest stages of development of the disorder. The vast majority of information regarding the first year of life in children with ASD comes from retrospective behavioral studies of videotapes of infants who later develop autism and prospective behavioral studies of infants who are at elevated risk for developing autism (e.g., Adrien, Lenoir, Martineau, Perrot, Hameury, et al., 1993; Baranek, 1999; Maestro, Muratori, Cavallaro, Pei, Stern, et al., 2002; Maestro, Muratori, Cesari, Cavallaro, Paziente, et al., 2005; Mitchell, Brian, Zwaigenbaum, Roberts, Szatmari, et al., 2006; Osterling & Dawson, 1994; Osterling, Dawson, & Munson, 2002; Volkmar, Chawarska, & Klin, 2005; Werner, Dawson, Munson, & Osterling, 2005; Zwaigenbaum, Bryson, Rogers, Roberts, Brian, & Szatmari, 2005). The results of these studies provide strong evidence that the social and communicative deficits associated with a diagnosis of autism between two and three years of age have developmental roots in the first year of life in a large percentage of children. For example, Osterling and Dawson (1994) scored previously recorded videotapes of first
birthday parties of children diagnosed with autism and typically developing controls and found that looking at the face of another person, showing, pointing, and failing to orient to name correctly classified 10 of 11 children with autism as having autism and 10 of 11 typically developing children as typically developing.

In terms of neurodevelopment, two studies have retrospectively examined head circumference measurements from medical records during the first two years of life and have found that head size (and presumably brain volume) of infants later diagnosed with autism is either of normal size or slightly smaller than normal in the first 6 months of life and then begins to grow larger than normal between 6 and 12 months (Courchesne, Carper, & Akshoomoff, 2003; Courchesne, Redcay, & Kennedy, 2004). These data suggest that, like social development, pathological structural neurodevelopment in autism may have roots in the first year of life. To date, however, there are no published studies on the functional neurodevelopment of autism in the first year of life.

Because the diagnosis of autism is based on impaired social and communicative functioning, much research has been focused on social processing and perception and the neural systems that underlie these abilities. One of the most commonly studied areas of social processing and perception in autism is that associated with human faces. Several decades of research have shown that autistic individuals exhibit a broad range of face processing deficits and abnormalities. They are impaired in the ability to recognize and match faces compared with non-face stimuli (Hauck, Fein, Maltby, Waterhouse, & Feinstein, 1998, Klin, Sparrow, de Bildt,
Cicchetti, Cohen, et al., 1999), fail to exhibit typical ‘face inversion effects,’ (Joseph & Tanaka, 2003; Langdell, 1978), are deficient at discriminating facial expressions of emotion (Deruelle, Rondan, Gepner, & Tardif, 2004; Weeks & Hobson, 1987), exhibit abnormal patterns of sensitivity to information in mouths versus eyes (Hobson, Ouston, & Lee, 1988), and exhibit abnormal patterns in the utilization of low-level visual information during face processing (Deruelle et al., 2004).

2.1.1 Face Processing in Normal Individuals

Neuroscience research has revealed face sensitive regions of temporal cortex in macaque monkeys using single-cell recordings during the presentation of static pictures of faces and non-face objects (Perrett, Rolls, & Caan, 1982; Abbott, Rolls, & Tovee, 1996). Evidence for face-specific regions in human cortex comes from analogous studies using both single neuron recordings (Allison & Bonds, 1994) and neuroimaging techniques (e.g., Kanwisher, McDermott, & Chun, 1997; Haxby, Ungerleider, Clark, Schouten, Hoffman, et al., 1999; Haxby, Hoffman, & Gobbini, 2002; Tzourio-Mazoyer, Schonen, Crivello, Reutter, Aujard, et al., 2002; Passarotti, Paul, Bussiere, Buxton, Wong, et al., 2003). The results of these studies have revealed an area on the underside of the temporal lobe along the lateral middle fusiform gyrus that is selectively activated by face stimuli and has thus been named the “Fusiform Face Area” (FFA). The finding that lesions in the FFA result in deficits in face recognition, i.e., “prosopagnosia,” provides additional evidence that the FFA is involved in face processing (e.g., Barton, Press, Keenan, & O’Connor, 2002).
Event-related potential (ERP) studies in adolescents and adults have identified a negative-going brainwave component recorded from electrodes over occipito-temporal cortex, the N170, that also shows face-selective responses. This commonly studied component, which peaks approximately 170 milliseconds following the presentation of a visual stimulus, is of larger amplitude and shorter latency in response to faces than to non-face objects (Bentin, Allison, Puce, Perez, & McCarthy, 1996). It also exhibits a ‘face inversion effect,’ with larger amplitude and slower latency responses to inverted than to upright faces but not objects (e.g., Rossion, Joyce, Cottrell, & Tarr, 1999). Finally, like responses in the FFA, the N170 response to faces is frequently larger over the right hemisphere than the left (Bentin, Deouell, & Soroker, 1999). Although there is current debate over the specific neural substrates of the N170, evidence suggests that it reflects activity from several cortical sources, including regions of the occipital and temporal cortices, and possibly including the FFA (e.g., David, Kiebel, Harrison, Mattout, Kilner, et al., 2006; Itier & Taylor, 2004; Joyce & Rossion, 2005; Rossion, Joyce, Cottrell, & Tarr, 2003).

Recent evidence from several ERP studies of face processing in the first year of life further suggests that two infant brainwave components recorded from scalp electrodes over occipito-temporal cortex, the N290 and the P400, specifically index the processing of human faces. The evidence for this is that these infant ERP components show shorter latencies for human faces than for monkey faces or non-face objects (Halit, de Haan, & Johnson, 2003), and shorter latencies for upright, as compared to inverted, human faces (de Haan, Pascalis, & Johnson, 2002; Halit et al.,
2003; Halit, Csibra, Volein & Johnson, 2004). They have also been found to exhibit some degree right-stronger-than-left and right-faster-than-left responses specific to human faces (Halit et al., 2003). Based on these data, it has been suggested that these two components may be developmental precursors to both the N170 component observed in adult subjects and the prN170 component observed in young children (de Haan, Johnson, & Halit, 2003; Halit et al. 2003).

2.1.2 Face Processing in Individuals with Autism

The results of functional magnetic resonance imaging (fMRI) studies indicate that individuals with ASD exhibit atypical face processing compared to that of typical subjects. For example, several studies have found reduced face-driven activity in the FFA in individuals with autism (e.g., Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Schultz, Gauthier, Klin, Fulbright, Anderson, et al., 2000). Although there is some evidence to suggest that reduced FFA activity in autism is restricted to unfamiliar faces (Aylward, Bernier, Field, Grimme & Dawson, 2004; Pierce, Haist, Sedaghat, & Courchesne, 2004), and may be an artifact of the experimental methods employed in studies in some cases (Hadjikhani, Joseph, Snyder, Chabris, Clark, et al., 2004), the majority of the fMRI results suggest that brain activity during face processing is atypical in this population (Schultz & Robbins, 2005). In addition to these fMRI data, data collected using ERPs have consistently revealed abnormalities in the early stages of face processing in autism (see Dawson, Webb, & McPartland, 2005 for review). For example, it has been shown that, compared to typically
developing controls, adults with ASD exhibit slower than normal peak N170 responses to faces but normal latency responses to objects (McPartland, Dawson, Webb, Panagiotides, & Carver, 2004). Individuals with autism also fail to show a ‘face inversion effect’ in the N170 component (McPartland et al., 2004). Abnormalities in early stages of face versus non-face processing have also recently been uncovered through the use of magnetoencephalography (MEG) (Bailey, Braeutigam, Jousmaki, & Swithenby, 2005).

Evidence for abnormalities in face processing early in life in autism comes from several ERP studies conducted by Dawson and colleagues (Dawson, Webb, Carver, Panagiotides, & McPartland, 2004; Dawson, Carver, Meltzoff, Panagiotides, McPartland, et al., 2002; Webb, Dawson, Bernier, & Panagiotides, in press). In one study, Dawson, Carver, and colleagues examined the neural correlates of familiar and unfamiliar face and object processing in 3- to 4-year old children with autism, children with developmental delays (DD), and typically developing children (TD) (Dawson, Carver, Meltzoff, Panagiotides, McPartland, et al., 2002). As expected, the ERPs of TD children differentiated between familiar and unfamiliar faces in two ERP components: The P400 recorded from electrodes over occipito-temporal cortex, and the Nc recorded from frontal and midline electrodes. Unlike these TD children, 3- to 4-year old ASD children did not show differentiation of familiar and unfamiliar faces in either of these ERP components. Like the TD children, however, they did show differential responses to familiar and unfamiliar objects in both the P400 and Nc. Control children with DD in this study did not show differential P400 or Nc responses
to familiar and unfamiliar faces or familiar and unfamiliar objects, but showed
differentiation of both in a positive component that followed the Nc, the Positive Slow
Wave (PSW), that neither the ASD nor the TD children did. These results suggest that
autism is associated with face recognition impairment early in life.

In a follow-up study, Webb et al. (in press), examined early stage face versus
object processing in 3- to 4-year old children with autism. To do so, they collapsed
the ERP data collected in the study of familiar and unfamiliar face and object
processing (described above), and analyzed an ERP component believed a
developmental precursor to the adult N170, which has thus been termed the prN170.
Statistical comparisons of prN170 responses revealed abnormal patterns of face and
object processing in the ASD children relative to children in the two control groups.
Specifically, the ASD children exhibited *larger* amplitude differentiation of face and
object processing than did children in either control group. Interestingly, this effect
was driven by more positive (i.e., *reduced*) response to the object stimulus in the ASD
children relative to control children. Comparisons of prN170 latencies also revealed a
significant interaction whereby TD children processed faces faster than objects, but
ASD children processed objects faster than faces. Unlike the TD or ASD children,
DD children showed similar latency prN170 responses to faces and objects. However,
the interaction between stimulus and group was still significant between the ASD
children (object latencies shorter than faces) and DD children (equal latency responses
to faces and objects). Because effects of familiarity on the prN170 were not
examined, it is possible that the observed effects were driven by an interaction among
familiarity, stimulus type, and the subject groups. Given that this is not the case, however, these data provide evidence that early stage face versus object processing is abnormal in autism, and also suggest that these abnormalities are characterized by significant differences in object processing in these children relative to controls.

2.1.3 Face Processing and Genetic Risk for Autism

Familial research on behavioral indicators in autism spectrum disorders indicates that familial risk is not restricted to inheritance of the specific disorder. Instead, family members have shown a broad phenotype, including low (but sub-clinical) performance on diverse indices of language, cognition, and communication (Fombonne, Bolton, Prior, Jordan, & Rutter, 1997; Le Couteur, Bailey, Goode, Pickles, Robertson, et al., 1996; Pickles, Starr, Kazak, Bolton, Papanikolaou, et al., 2000; Piven, Palmer, Landa, Santangelo, Jocabi, et al., 1997). Such results suggest a broad risk for social, communicative, and cognitive difficulties is inherited rather than a specific diagnosis (Plomin & Emde, 1993; Plomin & Kosslyn 2001; Plomin & Spinath 2002; Plomin & McGuffin 2003).

Recently, Dawson and colleagues studied brainwave responses to upright and inverted faces and objects in parents of children with autism and control participants (Dawson et al., 2005). They found that N170 responses were faster to faces than to objects in the control group, but not in the parents of children with autism. They also found that control participants exhibited right-stronger-than-left responses to faces but the parents of children with autism did not. These data indicate that abnormalities in
the early stages of face processing may be a functional trait marker for genetic risk for autism spectrum disorders (i.e., an endophenotypic marker).

In the current study, we tested the hypothesis that genetic risk for autism is associated with abnormalities in the early stages of face and/or object processing early in life. Specifically, we recorded ERPs in response to faces and non-face objects in 10-month old infant siblings of children diagnosed with autism and analyzed ERP components associated with the early stages of face and object processing during infancy (N290 and P400). The results of the study revealed significant differences between at-risk and control infants in the mean latency of responses to faces relative to objects in both of these components. Significant differences in the relative amplitude of the N290 responses to faces and objects were also found between the two groups. As in a recent study of face versus object processing in young children with autism, some of these group differences were driven by abnormalities in object processing in the ASD group. Overall, these results suggest that genetic risk for autism is associated with abnormalities in the early stages of face and object processing early in life. These data provide insight into the possible neurodevelopmental basis of familial risk for the social and communication deficits associated with autism and the broader autism phenotype.

2.2 Methods

2.2.1 Participants

Eighteen infant siblings of children diagnosed with autism spectrum disorders
(i.e., “at-risk” infants) and 36 infants with no family history of autism participated in the study. Data from 8 infant siblings of children with autism and 16 control infants were ultimately excluded from analysis due to failure to attend to a sufficient number of trials and/or excessive movement artifacts in the EEG. Therefore, the final numbers of subjects used for data analysis were 10 at-risk and 20 control infants. No child had a history of seizures or other medical or neurological disorder. At-risk infants were recruited from the local community via an outreach program in the greater San Diego area autism community, which included referrals from other UCSD laboratories conducting autism research, referrals from local service providers, and advertisements placed on websites and in local autism-related newsletters. The older sibling of the at-risk infants received an independent diagnosis of an autism spectrum disorder by a licensed clinical psychologist or medical doctor not associated with this research. Of the 10 at-risk infants included in the final analyses, 5 had an older sibling diagnosed with Autistic Disorder, 1 had an older sibling diagnosed with Aspergers Syndrome, and 4 had an older sibling diagnosed with Pervasive Developmental Disorder – Not Otherwise Specified. Five of the at-risk infants included in the final analyses were female (50%), and five were male (50%), and nine of the control infants were female (45%) and 11 were male (55%). Control infants were recruited through an infant subject pool that involved sending letters to new parents whose names are supplied to us by Vital Statistics in San Diego County. All infants were screened for evidence of neurological impairments, and visual or hearing impairments (via parent report). The mean age of the at-risk infants was 307 days, with a range of 295-315 and a standard
deviation of 5.4 days. The mean age of the control infants was 302 days, with a range of 278-325 and a standard deviation of 15 days. A one-tailed t-test confirmed that there was no difference in the age of the two groups of infants (p>0.05).

### 2.2.2 Stimuli

Stimuli consisted of four pictures, familiar and unfamiliar faces and familiar and unfamiliar objects (the objects being toys). The pictures were taken with a Canon 5.0 megapixel digital color camera. A picture of each infant’s mother’s (“familiar”) face was matched with another “unfamiliar” female face selected from mothers of other infants who participated in the study. Mothers were photographed with their clothing obscured by a gray scarf and with earrings and other jewelry removed. The unfamiliar face was chosen to be dissimilar from the mother’s face in terms of hair color, hairstyle, eye color, face shape, and facial features, e.g., size of nose, but of the same ethnicity. A picture of each infant’s favorite (“familiar”) toy was taken and matched with the “unfamiliar” favorite toy of another infant who participated in the study, with which the mother verified that her infant was unfamiliar. Pictures of toys were taken against the same gray background and digitally manipulated using Adobe Photoshop software (Adobe Systems, Inc., Mountain View, California, USA) to be of equal size when displayed on the computer monitor, while maintaining the toy’s original proportions. The familiar and unfamiliar toys were matched based on shape, color, and size, but were selected to have different functions (e.g., vehicle and non-vehicle).
2.2.3 ERP Recording

ERPs were recorded using a Geodesic Sensor Net consisting of 124 evenly distributed electrodes embedded in small sponges (Electrical Geodesics, Inc, Eugene, Oregon, USA). EEG was recorded continuously and referenced to a single vertex electrode (Cz). Signals were amplified using an Electrical Geodesics, Inc. NetAmps amplifier with a gain set to 10,000x, a sampling rate of 250 Hz, and a bandpass filter of 0.1-100 Hz. Impedences were checked on-line prior to recording and were considered acceptable when they were below 80 kOhms.

2.2.4 Apparatus and Procedure

After application of the sensor net, infants passively viewed the stimuli while seated on their parent’s lap in a dimly lit electrically and acoustically shielded chamber. Stimuli from each of the four conditions, familiar and unfamiliar faces and objects, were presented randomly intermixed with equal probability in a single block of trials. Stimuli were presented for 500 ms with an intertrial interval that varied randomly between 500 and 1200 ms. Infants were positioned approximately 65 cm from the stimulus presentation monitor, and were monitored by an experimenter in another room via a video camera located just above the stimulus presentation monitor and connected to a CCTV system. Online judgements were made by this experimenter regarding whether or not the infant was viewing the stimuli presented on the monitor, and button presses marked trials during which the infant was not
attending so that they would be excluded from analysis. Stimulus presentation continued until the infant became too fussy or bored to attend.

**2.2.5 ERP Waveform Analysis**

Continuous EEG recordings were processed off-line with a 40 Hz low-pass filter. The EEG was then divided into individual segments of 1300 ms (100 ms of pre-stimulus recording, 500 ms of stimulus presentation, and 700 ms of post-stimulus recording), and baseline corrected to the average voltage during the 100 ms prior to stimulus onset. Individual trials were inspected for eyeblinks and ocular-motor artifacts. Trials were also visually inspected and subsequently excluded from further analysis if they contained motion artifact such as head movements. Finally, trials were rejected if they contained more than 10 total bad channels. Of the remaining trials, individual bad channels were replaced using spherical spline interpolation. Individual subject averages were computed separately for the face and object stimuli (collapsing across familiarity), and then re-referenced to the average reference.

The average number of total trials used in the final analysis was 47.8 (SD = 15.2) for the at-risk infants and 48.6 (SD = 20.0) for the control infants. The average number of total face trials viewed was 24.4 (SD = 6.7) for at-risk and 24.1 (SD = 9.8) for the control infants; and the average number of total object trials viewed was 23.4 (SD = 8.8) for the at-risk and 24.6 (SD = 10.9) for the control infants. *T-Tests* conducted to compare the total number of trials, number of face trials, and number of object trials were all non-significant (p>0.05). In both groups, the percent of trials that
were familiar versus unfamiliar was approximately 50% in both the face and object conditions (range = 47.6% – 52.3%).

Inspection of the grand averaged waveforms revealed N290 and P400 components with scalp distribution, topography, and timing consistent with several previous studies of early face and non-face object processing in infancy. Electrode groupings for the right and left hemisphere were chosen based on visual inspection of both the grand-averaged and individually averaged ERP data. The electrode groupings, located on the regions of the scalp over the occipito-temporal cortex, were as follows: Right Hemisphere: 85, 86, 91, 92, 96, 97, 98, 101, and Left Hemisphere: 51, 57, 58, 59, 60, 64, 65, 66 (See Figure 2.1). Individualized time windows for the components were then selected for each subject based on examination of the topography of these components in the selected electrodes. The peak latency and amplitude of the N290 and P400 were then derived by averaging the peak amplitude and latency from each channel over the right and left hemispheres. Electrode grouping averages were then analyzed separately for each component using repeated measures ANOVAs with stimulus type (face, object) and hemisphere (left, right) as within-subjects factors and subject group (at-risk, controls) as a between-subjects factor, with Greenhouse-Geisser corrections when appropriate. Additional t-tests designed for two samples with unequal variance were also performed when warranted.

2.3 Results

2.3.1 N290 Amplitude
The N290 exhibited a stimulus by group interaction, whereby faces and objects were of the same amplitude in control infants but objects were of weaker amplitude than faces in the at-risk group (F = 4.504, p = .043; two-tailed t-test p = 0.026, and see Figures 2.2 and 2.3 for waveforms, and see Figure 2.4). There was also a hemisphere by group interaction whereby responses were more right-lateralized in the control infants than in the at-risk infants (F = 4.839, p = .036).

2.3.2 N290 Latency

The N290 exhibited an effect of stimulus whereby faces were processed slower than objects (F = 4.661, p = .040). Although there was not a significant interaction in the ANOVA, examination of the means indicates that this effect was driven, in part, by much faster processing of objects than faces in the at-risk group but approximately equal speed of processing faces and objects in the control infants (ASD t-test p = 0.020; and see Figure 2.5). The N290 also exhibited a hemisphere by group interaction, whereby at-risk infants exhibited faster processing in the right hemisphere than in the left but control infants showed the same speed of processing in both hemispheres (F = 4.510, p = .043).

2.3.3 P400 Amplitude

The P400 exhibited a hemisphere by group interaction whereby controls exhibited a strong left hemisphere advantage whereas at-risk infants exhibited a right hemisphere advantage (F = 9.279, p = .005). The P400 also exhibited a stimulus by
hemisphere interaction, whereby faces tended to be processed more in the left hemisphere than did objects (F = 7.650, p = .010).

2.3.4 P400 Latency

The P400 exhibited a stimulus by group interaction whereby faces were processed significantly faster than objects by the control infants, but at-risk infants processed objects faster than faces (F = 8.800, p = .006; t-tests; and see Figure 2.6).

2.4 Discussion

The present study was aimed at determining whether familial risk for autism is associated with abnormal brain activity during early stages of face versus object processing early in life. Our results indicated that young infant siblings of children with autism exhibited faster and larger amplitude N290 brain electrical responses to objects than control infants. These infants also showed a faster response to objects than to faces in a positive (P400) brain electrical response, while control infants exhibited the opposite pattern (i.e., faces faster than objects). These results support the hypothesis that genetic risk for autism is associated with abnormal brain activations in response to both faces and objects in the first year of life.

It is important to note that the data reported were collected in the context of an experiment designed to study face and object recognition memory and, therefore, the stimuli presented were familiar and unfamiliar faces (i.e., infant’s mom, stranger) and objects (i.e., infant’s favorite toy, unfamiliar toy). As a result, the differences in face
and object processing reported could be the result of an interaction among subject group, stimulus type, and familiarity, which was not visible to the analyses conducted. However, there are two things to be said about this. First, given the difficulty in recruiting and testing young infant siblings of children with autism, and given that no data have been published on brain functioning in families affected by autism in the first year of life, the data reported in the current study represent a novel and important first effort to examine face and object processing in this population. Second, any complex interaction involving familiarity as a variable would also have to include subject group as a variable in order to explain the group differences observed in the current study. Therefore, the possible presence of such an interaction should temper interpretations of the specific nature of the observed effects, but does not detract from the larger interpretation of the findings as evidence of abnormalities in face versus object processing early in life in families affected by autism.

The results of the current study of young infants from families affected by autism were remarkably similar to recently reported data collected from 3- to 4-year-old children diagnosed with autism employed highly similar methods and conducted analyses in the same manner (Webb et al., in press). As described earlier, the ASD children in this study exhibited prN170 responses that were of higher amplitude than those of control children. This same difference was observed between at-risk and control infants in N290 amplitudes in the current study. Webb and colleagues also observed an interaction among group and stimulus, whereby typical children processed faces and objects at the same speed but ASD children processed faces
slower than objects. Similarly, in the current study, typical infants processed faces and objects at the same speed, but at-risk infants processed objects faster than faces in the N290 component. Additionally, in the P400 component, typical infants processed faces faster than objects and at-risk infants processed objects faster than faces. Therefore, the relative patterns of face versus object processing were highly similar in these two studies. Because Webb and colleagues studied very young children and the methods for data collection and analysis are the most similar to ours, we interpret the striking similarities in our results as evidence that the abnormalities in face versus object processing in the at-risk infants observed in the current study are likely highly similar to those associated with a diagnosis of autism.

Given that our results truly represent abnormalities in the neural correlates of face and object processing associated with familial risk for autism during the first year of life, we suggest that these abnormalities could reflect reduced cortical specialization for face versus object processing and/or anomalies in the relative salience of face and object stimuli in these infants. These factors could put them at risk for impairments in social, communicative, and cognitive functioning such as that characteristic of autism and the broader autism phenotype later in life.

The data from the current study open up the possibility of using ERPs and other measures of brain functioning in an effort to identify autism in the first year of life. Although this is a possibility that will certainly be explored in the coming years, the results of the recent study of parents of ASD children conducted by Dawson and colleagues (Dawson et al., 2005) as well as the current study suggest that ERP
responses to face and object stimuli in unaffected first-degree relatives of individuals with autism appear to be highly similar to those of individuals diagnosed with autism. Therefore, measures of face processing will likely need to be supported by other measures of neural functioning and behavior in order to effectively aid in the identification of autism in early infancy.

In sum, the current study provides evidence for abnormalities in face and object processing in 10-month-old infants who are at risk for autism because they have an older sibling diagnosed with an ASD. These data provide important insights into the neurodevelopmental basis of impairments in face processing in families affected by autism, and provide preliminary support for the hypothesis that autism is characterized by abnormalities in cortical systems involved in face versus object processing early in life.

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References


Figure 2.1 **Left and right hemisphere electrode groups.** Darkened electrode locations represent the electrodes used in the N290 and P400 component analyses.
Figure 2.2 Scalp recorded ERP responses for at-risk infants for face and object stimuli. Data are collapsed across the left and right hemispheres. The N290 is the negative-going trough between approximately 170 and 320 ms. The P400 is the positive-going peak that follows between approximately 350 and 540 ms.
Figure 2.3 Scalp recorded ERP responses for control infants for face and object stimuli. Data are collapsed across the left and right hemispheres. The N290 is the negative-going trough between approximately 170 and 320 ms. The P400 is the positive-going peak that follows between approximately 350 and 540 ms.
Figure 2.4 Face minus object amplitude responses for the N290 component.

Control infants showed similar amplitude responses to face and object stimuli, but at-risk infants showed stronger responses to faces than objects. This effect was driven by weaker responses to objects in the ASD group relative to controls.
Figure 2.5 Face minus object latency responses for the N290 component. Control infants showed equal latency responses to faces and objects, whereas at-risk infants showed significantly shorter latency responses to objects relative to faces.
Figure 2.6 Face minus object amplitude responses for the P400 component.

Control infants showed equal amplitude responses to faces and objects, whereas at-risk infants showed significantly larger amplitude responses to objects than to faces.
Chapter 3

Abstract

A wealth of data has documented impairments in face processing in individuals with Autism Spectrum Disorders (ASD). Recently, the suggestion has been made that these impairments may arise from abnormal development of a subcortical face processing pathway that originates in the Magnocellular division of the visual system. To test this hypothesis, we employed select visual stimuli to measure the sensitivities of the Magnocellular (M) vs. Parvocellular (P) pathways in six-month-old infants who are at risk for ASD because they have an older sibling diagnosed with the disorder (“At-Risk infants”), and compared their data to typically developing controls (i.e., infants with no family history of ASD). Results indicate that At-Risk infants exhibit normal P pathway, yet abnormal M pathway, function. Given that ASD and its symptoms are known to run in families, these results suggest that autism may be associated with abnormal M pathway function early in infancy, which could aid in early diagnosis of the disorder in some cases.

3.1 Introduction

Autism spectrum disorders (ASD) are pervasive developmental disorders characterized by deficits in social and communication skills, which can currently be diagnosed between 24 and 36 months of age (Filipek, Accardo, Baranek, Cook, Dawson, et al., 1999). Decades of research on individuals diagnosed with ASD have
revealed abnormalities in a variety of social, communicative, and emotional behaviors (see Carter, Davis, Klin, & Volkmar, 2005 for review). Concomitant with this behavioral data, significant evidence has accumulated documenting neural abnormalities in brain regions associated with social processing and perception in individuals with ASD (Schultz & Robbins, 2005). In particular, a growing body of evidence suggests that there are significant abnormalities in the neural systems that underlie the visual processing and perception of faces in this population (Dawson, Webb, & McPartland, 2005; Schultz & Robbins, 2005).

In terms of early development, the results of several event-related potential (ERP) studies of 3- to 4-year-old children have revealed that abnormal brain activity during early stages of face processing is present very early in life in ASD (Dawson, Webb, Carver, Panagiotides, & McPartland, 2004; Dawson, Carver, Meltzoff, Panagiotides, McPartland, & Webb, 2002; Webb, Dawson, Bernier, & Panagiotides, in press). Simultaneously, data from retrospective behavioral studies of videotapes of infants who later develop autism suggest that deficits in attention to faces, voices, and other social and social-communicative stimuli in the first year of life are strong indicators of a later diagnosis of autism (e.g., Baranek, 1999; Maestro, Muratori, Cavallaro, Pei, Stern, et al., 2002; Maestro, Muratori, Cesari, Cavallaro, Paziente et al., 2005; Osterling & Dawson, 1994; Osterling, Dawson, & Munson, 2002; Volkmar, Chawarska, & Klin, 2005; Werner, Dawson, Munson, & Osterling, 2005). Consistent with this, prospective behavioral studies of infants who are at high risk for developing autism have also found differences in social measures in infants who later develop
autism and those who do not (e.g., Mitchell, Brian, Zwaigenbaum, Roberts, Szatmari, et al., 2006; Zwaigenbaum, Bryson, Rogers, Roberts, Brian, & Szatmari, 2005). Based on these data, numerous groups have suggested that deficits in face processing and perception and the neural systems that underlie it may play a critical role in the etiology of autism (e.g., Carver & Dawson, 2002; Dawson, Webb, Wijsman, Schellenberg, Estes, et al., 2005; Marcus & Nelson, 2001; Sasson, in press; Schultz, 2005).

3.1.1 Models of the Neurodevelopment of Face Processing

Perhaps the most prominent models of face processing impairments in autism are those that posit that reduced experience with faces early in life results in decreased specialization of neural systems involved in face processing (e.g., Carver & Dawson, 2002; Dawson et al., 2005; Marcus & Nelson, 2001). These models are based on converging behavioral and neuroimaging research that suggests that experience with faces is associated with specific developmental changes in perceptual sensitivities to faces (Bertin & Bhatt, 2004; Bhatt, Bertin, Hayden, & Reed, 2005; Friere & Lee, 2004) and complementary increases in neural specialization for face processing (e.g., de Haan, Johnson, & Halit, 2003; Gauthier & Nelson, 2001; Passarotti, Paul, Bussiere, Buxton, Wong, et al., 2003; Taylor, Batty, & Itier, 2004; Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999). For example, Pascalis, de Haan, and Nelson (2002) found that 6-month old infants were able to discriminate the identities of both human and monkey faces, but 9-month old infants and adults were only able to discriminate
human faces. More recently, Pascalis and colleagues showed that visual experience with monkey faces between 6 and 9 months of age resulted in a maintained ability to discriminate monkey faces at 9 months (Pascalis, Scott, Kelly, Shannon, Nicholson, et al., 2005). These results suggest that the ability to discriminate human faces is the result of continued experience with human faces and/or that perceptual narrowing to visual information that is specific to human faces inhibits sensitivity to monkey faces. Data from neuroimaging studies provide converging evidence that the developing brain shows increased specialization for faces and the visual information in them with experience (e.g., de Haan, Johnson, & Halit, 2003; Gauthier & Nelson, 2001; Passarotti, Paul, Bussiere, Buxton, Wong, et al., 2003; Taylor, Batty, & Itier, 2004). For example, early brainwave responses show a developmental progression reflective of changes in sensitivity to the familiar upright as compared to the unfamiliar inverted orientation of faces (de Haan, Johnson, & Halit, 2003; Taylor, Batty, & Itier, 2004). Data from functional Magnetic Resonance Imaging (fMRI) studies also suggest that brain activations to faces become increasingly localized and increasingly segregated from non-face processing with development (Passarotti et al., 2003). Because studies have found that individuals with autism do not show expected sensitivities to face stimuli (e.g., Joseph & Tanaka, 2003; McPartland, Dawson, Webb, Panagiotides & Carver, 2004) and have also uncovered evidence for decreased specialization and localization of face-specific processing in some studies (Dawson, Webb, & McPartland, 2005; Schultz & Robbins, 2005), this model has garnered significant support.
In terms of specific neural mechanisms that may underlie developmental impairments in the face expertise system in autism, two models have been proposed. In the first model, Dawson and colleagues proposed that decreased social attention early in life in autism may be the result of impairments in neural systems involved in establishing stimulus-reward relationships for social stimuli. This, they argue, would reduce spontaneous motivation to attend to faces over other stimuli, ultimately resulting in an impaired ability to develop important social affiliations that form the basis for learning a variety of social and communication skills (Dawson et al., 2005). This proposal originates from data that suggest that very young children with autism show specific impairments in the ability to establish stimulus-reward relationships mediated by areas of the orbito-frontal cortex and its connections with limbic structures such as the amygdala (Dawson, et al., 2002) as well as evidence for reduced plasma concentration of oxytocin (Modahl, Green, Fein, Morris, Waterhouse, et al., 1998), which is believed to be involved in the development of this reward system.

In a second model, Schultz (2005) suggested that failure to develop a normal face expertise system in ASD may be the result of the abnormal development of a subcortical face processing system in early infancy. This model is based on behavioral data that indicate that infants have a bias to attend to faces over non-face visual stimuli, and suggest that this bias is subserved by a subcortical visual system during the first two months of life (Morton & Johnson, 1991; Johnson, 2005; Simion, Valenza, Umilta, & Dalla Barba, 1998). Evidence from neurophysiological and psychophysical studies suggests that this visual system originates in the magnocellular
(M) pathway, which sends signals (via the superior colliculus, Perry & Cowey, 1984),
to the amygdala (Pasley, Mayes, & Schultz, 2004), which, in turn, has reciprocal
connections with cortical regions involved with face processing and perception (e.g.,
Amaral & Price, 1984). Because there are known structural abnormalities of the
amygdala in ASD (e.g., Howard, Cowell, Bourcher, Broks, Mays, et al., 2000),
Schultz suggested that these amygdala abnormalities disrupt the development of
normal face processing in ASD. Although Schultz (2005) suggested that
abnormalities in the amygdala are the most likely cause of the proposed subcortical
face processing abnormalities in autism, it is possible that these abnormalities may
arise from another part of this system subcortical visual system.

3.1.2 Neurophysiology of the visual pathways

The Magnocellular (M) and Parvocellular (P) subcortical visual pathways are
two of the three main pathways from the eye to the visual cortex (the third pathway
being the Koniocellular pathway, about which much less is known), and are believed
to underlie different visual abilities based on their distinct response properties.
Specifically, neurons of the M pathway are characterized by large receptive fields, fast
conduction velocities, transient responses, and high luminance (light/dark) sensitivity,
while neurons of the P pathway are characterized by small receptive fields, slow
conduction velocities, sustained responses and high chromatic (red/green) sensitivity
(see Dobkins, 2000 and Merigan & Maunsell, 1993 for details). Based on the
information gathered from these and other studies, researchers have been able to
examine the differential development of the M and P pathways in human infants by measuring developmental changes in sensitivity to visual information. Specifically, several studies have used psychophysical measures to document changes in sensitivity to luminance (light/dark) and red/green chromatic stimuli to elucidate the developmental trajectories of the M and P pathways, respectively (e.g., Dobkins, Anderson, & Lia, 1999).

In the current study, we investigated the possibility of abnormalities in M and/or P pathway function in ASD by examining visual sensitivities to luminance and red/green chromatic gratings in 6-month-old infants who are at risk for developing ASD because they have an older sibling diagnosed with an ASD (i.e., “At-Risk” infants). These infants have a roughly 16-fold greater risk of being diagnosed with ASD than control infants, since ASD has a strong genetic component (Zwaigenbaum, Thurm, Stone, Baranek, Bryson, et al., 2006). More importantly, although only a small proportion of At-Risk infants are expected to develop ASD, it is likely that this group of infants will exhibit abnormalities, because familial research has shown that neural and behavioral markers run in families and are not restricted to those diagnosed with ASD (e.g., Le Couteur, Bailey, Goode, Pickles, Robertson, et al., 1996; Fombonne, Bolton, Prior, Jordon, & Rutter, 1997; Piven, Palmer, Landa, Santangelo, Jacobi, et al., 1997; Hughes, Plumet, & Leboyer, 1999; Pickles, Starr, Kazak, Bolton, Papanikolaou, et al., 2000; Dawson et al., 2002; Micali, Chakrabarti, & Fombonne, 2004; Bishop, Maybery, Wong, Maley & Hallmayer, 2006; Constantino, Lajonchere, Lutz, Gray, Abbacchi, et al., 2006). For example, it is known that parents of children
with ASD exhibit brainwave response abnormalities in face processing, similar to those observed in ASD (Dawson et al., 2005). The results of our study revealed significant differences between At-Risk and control infants on the M pathway task only. Such findings suggest that abnormal M pathway functioning early in infancy may be a functional trait marker for genetic susceptibility to autism (i.e., an endophenotypic marker), and may also aid in the very early diagnosis of ASD in some children.

3.2 Methods

3.2.1 Participants

Twenty-two infant siblings of children with autism spectrum disorders (10 F, 12 M), referred to as “At-Risk” infants, and 133 control infants (54 F, 79 M) participated. The older siblings of the At-Risk group were diagnosed with Autistic Disorder (n = 12), Aspergers Syndrome (n = 1), or Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS, n = 9), based on DSM-IV criteria (American Psychiatric Association, 2000) by a clinical psychologist or medical doctor not associated with this research. The control group consisted of infants with no known family history of ASD. Male infants with a 25% or greater chance of dichromacy (based on family reports of incidences of colorblindness on the mother’s side) were excluded from the study. In addition, female infants with a 25% or greater chance of being a carrier for dichromacy were also excluded since their red/green color vision is unpredictable. (Specifically, it is known from adult studies that female carriers of
dichromacy exhibit aberrant red/green luminance matches, e.g. (Swanson, 1991; Crone, 1959).

Infants were tested at roughly six months of age. For the At-Risk infants, the mean age on the first day of testing was 185 days (range = 176 to 208, SD = 7.9). For the control infants, the mean age on the first day of testing was of 181 days (range = 168 to 191, SD = 5.2). For all infants, testing was completed within 10 days, but typically within 5 days. With the exception of 3 At-Risk and 7 control infants who were born prematurely, the rest were born within 14 days of their due date. For both groups, about 60% of the sample were male. All infants met a minimum number of trials criterion (N > 155 trials), and the mean number of trials obtained for At-Risk infants (257) and control infants (267) was not different (p = 0.26).

In addition to comparing data between the 22 At-Risk and 133 control infants, we also conducted a “matched control” analysis. This latter analysis was conducted because in our larger sample, there were significant differences between groups in mean age on the first day of testing (the At-Risk group was, on average, 3.7 days older, p = 0.005), maturity at birth, i.e., the extent to which birth date differed from their due date (the At-Risk group was, on average, 5.6 days less mature, p = 0.007), and in the percentage of infants who had an older sibling (while all At-Risk infants, by definition, had an older sibling, only half of our control infants did). This matched control analysis consisted of data from 13 At-Risk infants for whom we could find 2 matched controls each (26 total controls). Here, the At-Risk and control infants were
matched for gender, postnatal age, maturity (i.e., pre/post due date) and having an older sibling.

3.2.2. Stimuli

The stimuli employed in this study were designed to test the integrity of M and P pathway functioning. Specifically, we used luminance (light/dark) and chromatic (red/green) stimuli, because it is known that sensitivity to these stimuli is mediated by the M and P pathways, respectively (Lee, Pokorny, Smith, Martin, & Valberg, 1990; Lee, Martin, & Valberg, 1989; Smith, Pokorny, Davis, & Yeh, 1995). All stimuli were generated on a Nanao F2-21 monitor (1152 x 870 pixels, 75 Hz) driven by a PowerMac 7100 computer. The 8-bit video board allowed for 256 discrete levels of luminance. The voltage/luminance relationship was linearized independently for each of the three guns in the display (Cowan, 1983), using a PR-650 Colorimeter (Photoresearch). The PR-650 was used for photometric measurements to standardize to $V_\lambda$ isoluminance.

Stimuli were 0.27 cycles/degree horizontally-oriented sinusoidal gratings, with a temporal frequency of 4.2 Hz. These spatial and temporal frequencies were chosen because they are near the peak of the contrast sensitivity functions for young infants (e.g., Atkinson, Braddick, & Moar, 1977; Banks & Salapatek, 1978; Dobkins & Teller, 1997; Dobkins et al.,1999). At a viewing distance of 38 cm, stimuli subtended 11.1° by 11.1° of visual angle (a total of 3 cycles) and were centered 15° to the left or right of screen center. The mean luminance of the display was 12.6 cd/m² with a
mean chromaticity of 0.478, 0.425 in CIE color space. The illuminated portion of the video monitor subtended 59° by 45°. Chromatic red/green gratings were produced by sinusoidally modulating the red and green phosphors 180 degrees out of phase. The chromatic grating was set to the mean isoluminance point determined for 24 adult subjects tested with motion photometry (see Dobkins et al., 1999 for detailed methods). Luminance gratings were produced by sinusoidally modulating the red and green phosphors in phase. Contrast in these stimuli is defined as the cone contrast, i.e., the root mean squared contrast produced in the long-wavelength-selective (L) and long-wavelength-selective (M) cones in the eye (see Dobkins et al., 1999 for details).

3.2.3 Psychophysical Paradigm

In order to obtain contrast thresholds for chromatic and luminance gratings, we used the forced-choice preferential looking (FPL) technique (Teller, 1979) with the method of constant stimuli, as described in detail previously (see Dobkins & Teller, 1996). Briefly, an adult experimenter (author EA or one of 9 research assistants, all of whom were highly experienced in the FPL technique) held the infant 38 cm away from the front of the stimulus monitor in the view of a video camera aimed at the infant’s face. On each trial, the grating stimulus appeared on the left or right side of the video monitor (15° eccentricity), and the experimenter used cues such as the infant’s head turning and gazing behavior to judge the left vs. right location of the stimulus. Trials containing chromatic or luminance gratings were randomly presented across trials, with contrast also randomized across trials (luminance = 1.25% - 80%
cone contrast, chromatic: 0.30% – 24.7% cone contrast). Computer beeps provided feedback to the adult experimenter as to whether the response was correct/incorrect.

3.2.4. Data Analyses

To obtain contrast thresholds, for each infant, a psychometric curve was fit to chromatic and luminance data using Weibull functions and maximum likelihood analysis (Weibull, 1951; Watson, 1979). Upper asymptotes were fixed at 95% (which reflects the typical peak performance of infants tested with FPL) and contrast threshold was defined as the contrast yielding 72.5% correct performance (i.e., halfway between 50 and 95%). Contrast sensitivity was determined from the inverse of threshold (i.e., sensitivity = 1/threshold), and then logged, because log, but not linear, sensitivity values conform to a normal distribution (see Dobkins, Anderson, & Lia, 1999). In addition to determining absolute sensitivity, we also computed a chromatic vs. luminance sensitivity difference score for each infant: Log Luminance Sensitivity – Log Chromatic Sensitivity. The advantage of this difference score is that it factors out effects of attention/alertness (which could differ from infant to infant, and/or between subject groups), providing a metric of the relative sensitivity to the two stimulus types.

3.2.5 Autism Assessments

At both 24 and 36 months, all children are assessed for ASD with the Autism Diagnostic Observation Schedule, (ADOS) (Lord, Risi, Lambrecht, Cook, Leventhal,
et al., 2000), which is a play-based assessment designed to elicit behaviors (or lack of behaviors) associated with a diagnosis of ASD. Behaviors are scored in vivo, but the ADOS was also videotaped for reliability. If the child's ADOS score falls above the cutoff for ASD, the parent is asked to return for a another visit without the child for the *Autism Diagnostic Interview-Revised (ADI-R)* (Lord, Rutter, & Le Couteur, 1994), which is a 1.5 to 3 hour parent interview regarding the child's behaviors. Also, at 24 and 36 months, all children are tested using the *Mullen Scales of Early Learning* (Mullen, 1997) and the *Preschool Language Scale (PLS-IV)* (Zimmerman, Steiner, & Pond, 2002), which measures expressive and receptive language skills. The final ASD diagnosis is dependent on the results from all assessments (the ADOS, the ADI-R, the PLS-IV, and the Mullen). The cognitive age score on the Mullen must be at least 18 months for the ADOS result to be considered valid. Of the 155 subjects in this study, thus far 41 (34 control and 7 At-Risk) have been assessed for, but only two have been diagnosed with, ASD. Thus, we do not yet know the outcome of all infants in our study (although the total number of infants diagnosed with ASD is expected to be extremely low). Note that whenever an infant in our study is diagnosed with ASD, his/her data are removed from the group means and analyzed separately (see Results).

### 3.3 Results

#### 3.3.1 Luminance and Chromatic Contrast Sensitivities

Group mean log luminance and chromatic contrast sensitivities for 22 At-Risk (*white bars*) and 133 control (*grey bars*) infants are presented in Figure 3.1A (left...
The results of a 2-factor ANOVA (1 = subject group, 2 = stimulus type (luminance vs. chromatic)) yielded no significant main effects. However, the interaction between subject group and stimulus type was significant (F(1,153) = 7.17, p = 0.008). This interaction was driven by the fact that chromatic contrast sensitivity was the same for both groups, yet luminance contrast sensitivity was significantly greater in the At-Risk group (by 0.20 log units, or 1.6-fold, p = 0.024, 2-tailed t-test). This group difference can also be witnessed by calculating a “difference score” (Log Luminance Sens – Log Chromatic Sens) for each infant and then comparing mean difference scores between groups (which is identical to looking at the interaction term in the 2-factor ANOVA). Difference scores are presented in Figure 3.1A (right panel), for At-Risk (white bar) and control (grey bar) infants. As expected, the mean difference score for the At-Risk group (0.04) was markedly higher than that of the control group (-0.14). (Note that the actual value of the difference score itself is not particularly informative, but rather, whether the difference score varies between groups.) In sum, these data reveal altered luminance contrast sensitivity in infants at risk for ASD. Given the overlap in phenotype between individuals with ASD and their first-degree relatives, these results suggest that ASD is associated with abnormal processing of luminance contrast, which suggests abnormal M subcortical pathway function.

As mentioned in the Methods, the At-Risk and control infants differed in terms of their mean age on first day of testing, maturity at birth, as well as the fact that while all At-Risk infants had an older sibling (by definition), not all control infants did.
Thus, it was important to show that these factors did not affect the relative sensitivity to chromatic and luminance stimuli. In regression analyses performed on data obtained from the control infants (for which we had a large sample), we found that neither age nor maturity correlated with the difference score (age: \( r = 0.093, p = 0.287 \), maturity: \( r = 0.043, p = 0.62 \)). And, a 1-factor ANOVA showed no effect of whether an infant had or did not have an older sibling (\( p = 0.63 \)). These findings indicate that the significant difference between groups in the difference score was not driven by such factors. However, we did find effects of age on absolute sensitivity. That is, as expected, older infants were more sensitive (Luminance: \( r = 0.330, p < 0.0001 \), Chromatic, \( r = 0.318, p < 0.0001 \), 1-tailed). Although the At-Risk group was, on average, older than the control group, this cannot account for the observed contrast sensitivity differences between groups, since the age effect would be expected to elevate both luminance and contrast sensitivity in the At-Risk group, which was not the case. Nonetheless, to control for these differences (in age, maturity, having an older sibling) between groups, we conducted a second analysis on a subset of the data, which matched the At-Risk and control infants in these respects.

In Figure 3.2A, group mean data are shown for 13 At-Risk infants (white bars) and 26 infants matched on age, maturity, and gender (grey bars), i.e., we used 2 control infants for each At-Risk infant (left panel = log luminance and chromatic sensitivity data, right panel = difference scores). The results of a 2-factor ANOVA (1 = subject group, 2 = stimulus type (luminance vs. chromatic)) yielded no significant main effects. However, the interaction between subject group and stimulus type was
significant (F(1,37) = 6.69, p = 0.007, 1-tailed). As in the data presented in Figure 3.1A, this interaction was driven by the fact that chromatic contrast sensitivity was the same for both groups, yet luminance contrast sensitivity was significantly greater in the At-Risk group (by 0.24 log units, or 1.73-fold, p = 0.026, 1-tailed t-test). As expected, the mean difference score for the At-Risk group (0.10) was markedly higher than that of the control group (-0.18). Also note that group mean values (both sensitivity values and differences scores) obtained in these matched control analyses were almost identical to those obtained in the larger more inclusive analyses. In sum, the results from these matched control analyses indicate that the effects seen in the original analyses were not driven by the effects of age at testing, maturity, or having an older sibling, lending further support to the notion that ASD is associated with abnormal M pathway function.

Of the 155 subjects in this study, thus far 41 (34 control and 7 At-Risk) have been assessed for, but only two have been diagnosed with, ASD (see Methods). One of these infants was a control infant. He was diagnosed with Autistic Disorder, via administration of the ADOS (Lord et al., 2000), the ADI-R (Lord et al., 1994), the PLS-IV (Zimmerman et al., 2002), and the Mullen (Mullen, 1997) at both 24 and 36 months of age in our laboratory. This diagnosis was also verified by a licensed clinical psychologist not associated with this research. Amazingly, he exhibited extremely high luminance contrast sensitivity, ~0.29 log units (i.e., 1.9-fold) greater than the mean for control infants, yet his chromatic contrast sensitivity was close to the mean for the control group. Accordingly, his difference score (0.15) was much higher than
the mean for control infants, and even higher than the mean for At-Risk infants. To demonstrate this effect, his difference score is plotted along with the group means in Figure 3.2B (grey circle). Another infant, who was an At-Risk infant, was diagnosed with *Autistic Disorder* at 24 months of age via the same assessment battery described above. For him, luminance sensitivity was in the control range, and chromatic sensitivity was lower than that of control infants. However, his difference score (-0.08) was nonetheless higher than the mean for control infants (Figure 3.2B, white triangle). The differences we observed between the two infants who went on to develop ASD are perhaps not surprising as we know that there is considerable variability in ASD and even evidence for subtypes (e.g., Milne et al., 2006). More data from infants who go on to develop ASD will be required to determine the significance of inter-subject differences.

3.4 Discussion

The data from our study provide the first demonstration that familial risk for ASD is associated with abnormal processing of luminance contrast in early infancy. Because luminance sensitivity is mediated by the M subcortical pathway, these results suggest that abnormal M pathway function could be an endophenotypic marker for ASD. It is important to point out that the fact that the At-Risk infants show enhanced luminance contrast sensitivity strongly suggests that the observed group differences are not driven by some sort of general delayed development in the At-Risk group (because a delay would predict the opposite result, i.e., poor luminance contrast
sensitivity). Along a similar line, our results cannot be due to differences in attention or alertness between groups, because any attention effects would be expected to alter both luminance and chromatic sensitivity, which was not the case. In addition, we point out the perceptual effects observed in our study of ASD are different from those seen in dyslexia or Williams Syndrome, which report decreased perceptual sensitivity associated with M pathway function (Demb, Boynton, Best, & Heeger, 1998; Atkinson et al., 1997).

We believe that the M pathway abnormality associated with ASD could alter the visual world of infants from families with ASD, putting them at risk for visuo-perceptual abnormalities, which in turn, could lead to widespread problems. More specifically, we suggest that M pathway abnormalities during development could be tied to the face processing deficits observed in ASD and their family members (Dawson, et al., 2005. In line with this notion, Schultz (2005) suggested that the face processing deficit in ASD may arise from abnormal development of a subcortical face processing system, which young infants are believed to rely on before the more mature cortical face processing system has fully developed (Johnson, 2005). This subcortical face processing system is thought to provide fast visual input to the amygdala, a limbic system structure involved in processing emotion, including facial expressions. The system originates in the M pathway, which sends signals (via the superior colliculus (Perry & Cowey, 1984), to the amygdala (Pasley, Mayes, & Schultz, 2004; Morris, 2001), which, in turn, makes reciprocal connections with face processing networks in visual cortex (Amaral & Price, 1984). Because there are known structural
abnormalities of the amygdala in ASD (Howard et al., 2000), Schultz suggested that these amygdala abnormalities disrupt the development of normal face processing. We extend this idea by suggesting that the known amygdala abnormalities in ASD could be secondary to (or concomitant with) abnormalities in the M pathway that feeds it (and see Deruelle, Rondan, Gepner, & Tardif, 2004 for evidence that individuals with ASD exhibit abnormally low reliance on M pathway signals for the processing of faces). Thus, like Schultz, we suggest that in the absence of effective signaling from the M pathway to the amygdala to face areas, cortical regions responsible for social cognition may fail to develop normally, resulting in the deficits in social, communicative, and emotional behaviors associated with ASD. In addition to this hypothesis, it is possible that abnormalities in M pathway processing in early infancy may affect visual processing of face (and perhaps other social) stimuli in a more stimulus driven way, for example, by attracting infants to attend to certain types of visual stimuli at the expense of attending to faces, or to attend to less socially relevant aspects of the face (like the moving mouth) rather than the eyes (Klin, Jones, Schultz, & Volkmar, 2003).

On a final note, it is worth pointing out that altered luminance contrast sensitivity (reflecting altered M pathway functioning) has not been observed in studies of older children (youngest age tested = 9 years) or adults with ASD (Bertone, Mottron, Jelenic, & Faubert, 2005; Pellicano, Gibson, Maybery, Durkin, & Badcock, 2005). We suggest that the differences between studies -- abnormal M pathway functioning at six months (as suggested by our results in At-Risk infants) yet normal
M pathway functioning by about nine years (as revealed in children and adults with ASD), can be reconciled with the following proposal. Abnormalities in the early-developing subcortical M pathway have negative consequences for neural areas that receive input and rely on the M pathway during a critical period of development, even if the M pathway attains normal functioning later in life. A similar phenomenon has been reported in studies that track the development of low- and high-level visual function in infants who were visually deprived (due to cataracts) in the first few months of life. These infants exhibit below normal contrast sensitivity when the cataracts are first removed (between 1 – 9 months (Mayer, Moore, & Robb, 1989; Harwerth, 1983), and although these low-level visual deficits resolve later on in life (at least for low to middle spatial frequencies (Ellemberg, Lewis, Maurer, Lui, & Brent, 1999), the early visual deprivation of these infants appears to produce impairments in higher-level visual function, such as holistic face processing and higher-order motion perception, later on in childhood (Lewis & Maurer, 2005). In a similar vein, we suggest that, in ASD, abnormalities in low-level visual processing early in life could be related to higher-level, cognitive deficits observed later on in life.

In sum, the current study provides the first demonstration of abnormalities in the M visual pathway in the first year of life associated with ASD, which could be used as an endophenotypic marker for the disorder. We are tracking the development of the infants in our study (both At-Risk and controls) to see whether M pathway function correlates with assessments of face vs. object processing, as well as other assessments of social, cognitive, communicative, and emotional behaviors, later in
life. From a clinical standpoint, we hope that the visual sensitivity measure of the current study, used in combination with other measures, could aid in early diagnosis of ASD in some children.

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References


Figure 3.1 Group luminance and chromatic data. *Left Panels.* Log contrast sensitivity for luminance (M pathway) and chromatic (P pathway) stimuli, for At-Risk (*white bars*) and Control (*grey bars*) infants. *Right Panels.* Difference Scores (Log Luminance – Log Chromatic). Error bars denote standard errors of the means. (A) Data from All Infants. (B) Data from infants in the Matched Control Analysis. The *grey circle* and *white triangle* represent difference scores from a control infant and an At-Risk infant, respectively, both of whom were later diagnosed with ASD (see text for details).
Chapter 4

I conducted three experiments in an effort to examine the roles of social and non-social factors in the neurodevelopment of autism. The first of these experiments was an examination of the neural correlates of semantic integration of words and environmental sounds within a picture context in young children diagnosed with autism. The purpose of this experiment was to determine whether semantic processing impairments in children with autism are limited to the social domain or whether they represent a more general semantic processing deficit that affects both the social and non-social domains. The second and third experiments involved electrophysiological assessments of face and object processing and a psychophysical assessment of magnocellular versus parvocellular functioning in young infant siblings of children with autism, respectively. These experiments were designed to capitalize on the broad genetic risk associated with autism to explore neurodevelopmental risk factors related to social and non-social functioning in the first year of life.

The results of experiment one showed that children with autism were impaired in the semantic integration of words, but not environmental sounds, within a picture context. We interpreted these data as evidence that semantic processing impairments may be limited to, or more severe in, the social domain in these children. These data, therefore, contribute to a wealth of evidence collected in other areas of cognitive functioning that suggest that autism may be the result of a relatively specific dysfunction in neural systems that underlie social processing and perception.
The results of experiment two showed that the 10-month-old infants with a sibling diagnosed with autism in our study exhibited atypical processing of faces and objects. Specifically, these infants exhibited faster responses to objects than to faces in two early-stage brain electrophysiological components (N290, P400), whereas infants with no family history of autism exhibited equal speed responses to faces and objects in one of these components and faster responses to faces than to objects in the other. Additionally, infants at risk for autism exhibited reduced responses to object stimuli relative to control infants in an early negative-going brain electrical component (N290). These data provide evidence that familial risk for autism is associated with abnormalities in face and object processing very early in life and, therefore, I interpreted these results as evidence that autism may have its neurodevelopmental roots in atypical specialization of non-social versus social processing.

The results of experiment three showed that the 6-month-old infants with a sibling diagnosed with autism in our study exhibited abnormalities in magnocellular, but not parvocellular, visual pathway functioning. Specifically, these infants exhibited enhanced sensitivity to luminance contrasts relative to control infants. These data support the hypothesis that familial risk for autism is associated with abnormality in an early-developing visual-sensory pathway that is believed to play a critical role in the development of cortical systems involved in face processing and perception. I interpreted these results as evidence that abnormalities in the neural systems that underlie social processing and perception in children and adults diagnosed with autism
may actually have neurodevelopmental roots in abnormal development of low-level sensory perceptual systems.

Together, the data collected in these studies provide important insights into the roles social and non-social factors may play in the functional neurodevelopment of autism. While the results of experiment one provide additional support for the hypothesis that disordered functioning in young children diagnosed with autism can largely be characterized by impairments in the neural systems that underlie social processing and perception, the results of both experiments two and three suggest that these abnormalities may actually arise from developmental abnormalities in sensory and perceptual systems that subserve both social and non-social functioning early in life. Because experiments two and three examined neurodevelopmental risk for autism and did not involve direct assessments of groups of infants who later developed autism, the implications of the results of these two experiments for the neurodevelopment of autism should be interpreted with caution. On the other hand, however, because the hypotheses tested in both of these experiments were strongly rooted in prominent theories of pathological neurodevelopment in autism, it is clear that continued research into these mechanisms will be critical for furthering our understanding of the neurodevelopmental basis of autism and related developmental disorders. This line of research also has clear implications for more general aspects of neural functioning. Most notably, it has implications for the relationships of early sensory-perceptual development and later cognitive functioning, as well as the neurodevelopmental relationships of social and non-social processing and perception.